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Examiner # (Mandatory): 76562 Requester's Full Name: Ram Shukla

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Serial Number: 09/578453 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention Pharmaceutical Composition and Utilization thereof

Inventors (please provide full names): Jacques Mallet et al

Earliest Priority Date: 9/29/94 Parent 08/624,469 PCT/FR94/01142

Keywords (include any known synonyms registry numbers, explanation of initialisms):

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SR ID NO. 2

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RUSH

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Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

RUSH

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Searcher: _____

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Date Picked Up: 12/21/01

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1 N.A. Sequence

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_____ Structure (#)

_____ Bibliographic

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_____ Fulltext

_____ Procurement

_____ Other

Vendors (include cost where applicable)

_____ STN

_____ Questel/Orbit

_____ Lexis/Nexis

_____ WWW/Internet

_____ In-house sequence systems (list)

_____ Dialog

_____ Dr. Link

_____ Westlaw

XX Other (specify)

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     (FILE 'HOME' ENTERED AT 16:50:51 ON 21 DEC 2001)

     FILE 'MEDLINE' ENTERED AT 16:50:59 ON 21 DEC 2001
L1             34 S VAL135
L2          22785 S P53
L3             32 S L1 AND L2
L4             32 S L1 (L) L2
L5              5 S L4 NOT PY>1993
L6           2712 S ADENOVIR? VECTOR
L7              0 S L1 (L) L2 (L) L6

     FILE 'CAPLUS' ENTERED AT 16:56:55 ON 21 DEC 2001

=> s l4
             34 VAL135
          19025 P53
L8            31 L1 (L) L2

=> s l8 not py>1993
        6321590 PY>1993
L9             5 L8 NOT PY>1993

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10            5 DUP REM L9 (0 DUPLICATES REMOVED)

=> d 1-5 ibib abs
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ENTRY DATE: Entered STN: 19931008
Last Updated on STN: 19931008
Entered Medline: 19930923

AB The wild-type (wt) p53 protein has transcriptional activation functions which may be linked to its tumor suppressor activity. Many **mutant p53** proteins expressed in cancers have lost the ability to function as transcriptional activators and furthermore may inhibit wt p53 function. To study the mechanisms by which mutant forms of p53 have lost their transactivation function and can act in a dominant negative manner, a structure-function analysis of both mutant and engineered truncated forms of p53 was carried out. We show that different **mutant p53** proteins found in cancers vary in the ability to inhibit the transcriptional transactivation and specific **DNA binding** activities of wt human p53. This transdominant effect was mediated through the carboxy-terminal oligomerization region. The role of the transactivation activity in transformation suppression by wt p53 was also examined by constructing an N-terminal deletion mutant lacking the transactivation domain. This mutant was unable to transactivate but could bind specifically to DNA. Although it was impaired in its ability to suppress transformation of primary rat embryo fibroblasts by **adenovirus** E1A plus activated ras, the N-terminal deletion mutant still had some suppression activity, suggesting that additional functions of p53 may contribute to transformation suppression.

L9 ANSWER 4 OF 4 MEDLINE
ACCESSION NUMBER: 92310577 MEDLINE
DOCUMENT NUMBER: 92310577 PubMed ID: 1614538
TITLE: Wild-type p53 activates transcription in vitro.
COMMENT: Comment in: Nature. 1992 Jul 2;358(6381):15-16
AUTHOR: Farmer G; Bargonetti J; Zhu H; Friedman P; Prywes R; Prives C
CORPORATE SOURCE: Department of Biological Sciences, Columbia University, New York 10027.
SOURCE: NATURE, (1992 Jul 2) 358 (6381) 83-6.
Journal code: NSC; 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920807
Last Updated on STN: 19970203
Entered Medline: 19920730

AB The p53 protein is an important determinant in human cancer and regulates the growth of cells in culture. It is known to be a sequence-specific **DNA-binding** protein with a powerful activation domain, but it has not been established whether it regulates transcription directly. Here we show that intact purified wild-type human and murine p53 proteins strongly activate transcription in vitro. This activation depends on the ability of p53 to bind to a template bearing a p53-binding sequence. By contrast, tumour-derived **mutant p53** proteins cannot activate transcription from the template at all, and when complexed to wild-type p53, these mutants block transcriptional activation by the wild-type protein. Moreover, the simian **virus** 40 large T antigen inhibits wild-type p53 from activating transcription. Our results support a model in which p53 directly activates transcription but this activity can be inhibited by **mutant p53** and SV40 large T antigen through interaction with wild-type p53.

=> d his

(FILE 'HOME' ENTERED AT 14:05:20 ON 21 DEC 2001)

FILE 'MEDLINE' ENTERED AT 14:05:30 ON 21 DEC 2001

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     FILE 'MEDLINE, CAPLUS' ENTERED AT 14:05:35 ON 21 DEC 2001
L1        622358 S VIRUS OR ADENOVIRUS OR ADENO-ASSOCIATED VIRUS OR HERPES VIRUS
L2        624092 S VIRUS OR ADENOVIRUS OR ADENO-ASSOCIATED VIRUS OR HERPES VIRUS
L3          3111 S MUTANT P53
L4             2 S DNA BIND DOMAIN
L5        103063 S DNA BIND? DOMAIN OR DNA BIND?
L6          6781 S L2 (L) L5
L7            29 S L2 (L) L5 (L) L3
L8            15 DUP REM L7 (14 DUPLICATES REMOVED)
L9             4 S L8 NOT PY>1994

=> s neuro? cell
L10       40920 NEURO? CELL

=> s l2 (L) l5 (L) l3 (L) l10
L11           0 L2 (L) L5 (L) L3 (L) L10

=> s  cell death or apoptosis
L12      131064 CELL DEATH OR APOPTOSIS

=> s l2 (L) l5 (L) l3 (L) l12
L13           7 L2 (L) L5 (L) L3 (L) L12

=> s  cell death or apoptosis or degeneration
L14      211949 CELL DEATH OR APOPTOSIS OR DEGENERATION

=> s l2 (L) l5 (L) l3 (L) l13
L15           7 L2 (L) L5 (L) L3 (L) L13

=> dup rem l15
PROCESSING COMPLETED FOR L15
L16           4 DUP REM L15 (3 DUPLICATES REMOVED)

=> d 1-4 ibib abs

L16  ANSWER 1 OF 4     MEDLINE                              DUPLICATE 1
ACCESSION NUMBER:   2000236965     MEDLINE
DOCUMENT NUMBER:    20236965   PubMed ID: 10777207
TITLE:              Wild-type p53 transactivates the KILLER/DR5 gene through an
                    intronic sequence-specific DNA-binding site.
AUTHOR:             Takimoto R; El-Deiry W S
CORPORATE SOURCE:   Laboratory of Molecular Oncology and Cell Cycle Regulation,
                    Howard Hughes Medical Institute, University of Pennsylvania
                    School of Medicine, Philadelphia 19104, USA.
CONTRACT NUMBER:    P01 CA75138-01 (NCI)
SOURCE:             ONCOGENE, (2000 Mar 30) 19 (14) 1735-43.
                    Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY:       ENGLAND: United Kingdom
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200006
ENTRY DATE:         Entered STN: 20000616
                    Last Updated on STN: 20000616
                    Entered Medline: 20000608
AB   KILLER/DR5, a tumor necrosis factor-related apoptosis-inducing
     ligand (TRAIL) death receptor gene, has been shown to be induced by DNA
     damaging agents and radiation in a p53-dependent manner. Although TRAIL is
     a potential therapeutic agent for cancer, the induction mechanism of its
     receptors is poorly understood. Here we show the identification of three
     p53 DNA-binding sites in the KILLER/DR5 genomic locus
     located upstream (BS1; -0.82 Kb) of the ATG site, within Intron 1 (BS2;
     +0.25 Kb downstream of the ATG) and within Intron 2 (BS3; +1.25 Kb
     downstream of the ATG). A modified p53-binding and immunoselection
     protocol using a wild-type p53-expressing adenovirus vector
     (Ad-p53) was used to identify the binding sites and to show that each
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binding site can bind specifically to wild-type p53 protein (wt-p53). A reporter assay revealed that only BS2 could enhance luciferase expression driven by a basal promoter. We constructed a reporter plasmid carrying the genomic regulatory region of KILLER/DR5 including the three p53 **DNA-binding** sites but no additional basal promoter. The genomic fragment showed basal transcriptional activity which was induced by wt-p53 but not by **mutant p53**, and human papilloma **virus** E6 inhibited the p53-dependent activation. Mutation of BS2 abrogated not only the binding activity of wt-p53 but also the induction of the KILLER/DR5 genomic promoter-reporter gene, indicating that BS2 is responsible for the p53-dependent transactivation of KILLER/ DR5. In p53-wild-type but not -mutant or -null cell lines, doxorubicin treatment stabilized p53 protein, and increased specific binding to BS2 as revealed by EMSA, and upregulated the KILLER/DR5 promoter-luciferase reporter gene. These results suggest that the transactivation of KILLER/DR5 is directly regulated by exogenous or endogenous wt-p53 and establishes KILLER/DR5 as a p53 target gene that can signal apoptotic death.

L16 ANSWER 2 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999263010 MEDLINE
DOCUMENT NUMBER: 99263010 PubMed ID: 10330179
TITLE: Btf, a novel death-promoting transcriptional repressor that interacts with Bcl-2-related proteins.
AUTHOR: Kasof G M; Goyal L; White E
CORPORATE SOURCE: Center for Advanced Biotechnology and Medicine, Rutgers University, Piscataway, New Jersey 08854, USA.
CONTRACT NUMBER: CA53370 (NCI)
CA64807 (NCI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1999 Jun) 19 (6) 4390-404. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF249273
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990617

AB The **adenovirus** E1B 19,000-molecular-weight (19K) protein is a potent inhibitor of **apoptosis** and cooperates with E1A to transform primary rodent cells. E1B 19K shows sequence and functional homology to the mammalian antiapoptotic gene product, Bcl-2. Like Bcl-2, the biochemical mechanism of E1B 19K function includes binding to and antagonization of cellular proapoptotic proteins such as Bax, Bak, and Nbk/Bik. In addition, there is evidence that E1B 19K can affect gene expression, but whether this contributes to its antiapoptotic function has not been determined. In an effort to further understand the functions of E1B 19K, we screened for 19K-associated proteins by the yeast two-hybrid system. A novel protein, Btf (Bcl-2-associated transcription factor), that interacts with E1B 19K as well as with the antiapoptotic family members Bcl-2 and Bcl-xL but not with the proapoptotic protein Bax was identified. btf is a widely expressed gene that encodes a protein with homology to the basic zipper (bZip) and Myb **DNA binding domains**. Btf binds DNA in vitro and represses transcription in reporter assays. E1B 19K, Bcl-2, and Bcl-xL sequester Btf in the cytoplasm and block its transcriptional repression activity. Expression of Btf also inhibited transformation by E1A with either E1B 19K or **mutant p53**, suggesting a role in either promotion of **apoptosis** or cell cycle arrest. Indeed, the sustained overexpression of Btf in HeLa cells induced **apoptosis**, which was inhibited by E1B 19K. Furthermore, the chromosomal localization of btf (6q22-23) maps to a region that is deleted in some cancers, consistent with a role for Btf in tumor suppression. Thus, btf may represent a novel tumor suppressor gene residing in a unique pathway by which the Bcl-2 family can regulate **apoptosis**.

L16 ANSWER 3 OF 4 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998156627 MEDLINE
DOCUMENT NUMBER: 98156627 PubMed ID: 9496913
TITLE: Characterization of rare p53 mutants from carcinogen-treated albumin-simian virus 40 T-antigen transgenic rats.
AUTHOR: Haas M J; Pitot H C
CORPORATE SOURCE: Department of Oncology, Medical School, University of Wisconsin, Madison 53706, USA.
CONTRACT NUMBER: CA07175 (NCI)
CA22484 (NCI)
CA45700 (NCI)
SOURCE: MOLECULAR CARCINOGENESIS, (1998 Feb) 21 (2) 128-34.
Journal code: AEQ; 8811105. ISSN: 0899-1987.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 19980326
Entered Medline: 19980318

AB The p53 gene has been either mutated or deleted in most human tumors examined to date. Mutations in the specific **DNA-binding domain** are the most common p53 mutations and are of interest because they may produce p53 molecules with transcriptional capabilities unlike those of the wild-type (WT) p53 protein. Mutations in the rat p53 gene were found in hepatic neoplasms of carcinogen-treated transgenic rats that express simian **virus** 40 (SV40) large T-antigen (TAg). Because this result was unexpected, we examined some of the biochemical and biological properties of the mutant proteins. Corresponding nucleotide changes were made by site-directed mutagenesis of the rat p53 cDNA, which was then inserted into a eukaryotic expression vector and transfected into the human hepatocyte cell line Hep 3B. Four of the **mutant p53** molecules from rat hepatomas retained a strict WT conformation. Two others existed in both WT and mutant conformations. All of the mutant proteins were able to bind TAg as well as WT p53 did. Whereas the WT p53 protein was able to repress expression of a reporter gene containing a p53-response element (pSV2CAT), the missense-**mutant p53** proteins induced transcription of the reporter to an extent equivalent to that of TAg. The mutant proteins also allowed TAg to induce the pSV2CAT reporter gene. The mutant molecules were able to enhance survival of Hep 3B cells, perhaps by preventing **cell death**, whereas expression of the WT p53 protein caused a reduction in cell number to nearly 10% of control levels. The results of these experiments suggest that the **mutant p53** molecules observed in the carcinogen-treated transgenic rats may have unique properties that are important in carcinogenesis.

L16 ANSWER 4 OF 4 MEDLINE
ACCESSION NUMBER: 97353069 MEDLINE
DOCUMENT NUMBER: 97353069 PubMed ID: 9209327
TITLE: Pathogenesis of Friend leukemia virus.
AUTHOR: Ikawa Y
CORPORATE SOURCE: Department of Retroviral Regulation, Tokyo Medical and Dental University Medical Research Division, Japan.
SOURCE: LEUKEMIA, (1997 Apr) 11 Suppl 3 152-4.
Journal code: LEU; 8704895. ISSN: 0887-6924.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 19970813

Entered Medline: 19970807

AB Friend leukemia **virus** complex (FLV) consists of replication-defective, Friend spleen focus-forming **virus** (F-SFFV) and replication-competent, Friend murine leukemia **virus** (F-MuLV). We produced transgenic mice possessing F-SFFV gp55 gene and clarified that the gp55 glycoprotein encoded by F-SFFV env-related gene is, by itself, responsible for the initiation of erythroleukemia. The occurrence of erythroleukemia, however, is sporadic in these mice. Erythroleukemia cell lines established from these mice possessed mutations in the p53 allele. One had a temperature-sensitive **mutant** **p53** allele, p53Val-135 and showed induction of **apoptosis** by expressing a wild-type p53 protein at 32 degrees C. Superinfection of the mice with Moloney murine leukemia **virus** (Mo-MuLV) conferred 100% induction of erythroleukemia, mutating p53 gene or activating Spfi-1 gene by insertional events. Activation of the JAK/STAT pathway, which is involved in cytokine signaling, was investigated in the gp55 signaling mediated by the erythropoietin receptor. JAK1 and STAT5 were constitutively tyrosine-phosphorylated but the **DNA** **binding** activity of STAT5 was not induced.

=> d his

(FILE 'HOME' ENTERED AT 14:05:20 ON 21 DEC 2001)

FILE 'MEDLINE' ENTERED AT 14:05:30 ON 21 DEC 2001

FILE 'MEDLINE, CAPLUS' ENTERED AT 14:05:35 ON 21 DEC 2001

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L1       622358 S VIRUS OR ADENOVIRUS OR ADENO-ASSOCIATED VIRUS OR HERPES VIRUS
L2       624092 S VIRUS OR ADENOVIRUS OR ADENO-ASSOCIATED VIRUS OR HERPES VIRUS
L3         3111 S MUTANT P53
L4            2 S DNA BIND DOMAIN
L5       103063 S DNA BIND? DOMAIN OR DNA BIND?
L6         6781 S L2 (L) L5
L7           29 S L2 (L) L5 (L) L3
L8           15 DUP REM L7 (14 DUPLICATES REMOVED)
L9            4 S L8 NOT PY>1994
L10       40920 S NEURO? CELL
L11           0 S L2 (L) L5 (L) L3 (L) L10
L12      131064 S  CELL DEATH OR APOPTOSIS
L13           7 S L2 (L) L5 (L) L3 (L) L12
L14      211949 S  CELL DEATH OR APOPTOSIS OR DEGENERATION
L15           7 S L2 (L) L5 (L) L3 (L) L13
L16           4 DUP REM L15 (3 DUPLICATES REMOVED)
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that a v-myc retrovirus (J3)-induced T-cell lymphoma line (J3D) has lost one of its **p53** alleles, whereas the other has become inactivated due to the insertion of a Moloney murine leukemia provirus in intron 4 with an opposite transcriptional orientation. No **p53** protein could be detected by immunoprecipitation with monoclonal anti-**p53** antibodies. We have transfected this line with the temperature-sensitive murine **Val135** construct that is expressed as mutant **p53** at 37 degrees C and largely wild-type **p53** at 32 degrees C. There was no difference in the number of viable cells among the **p53** transfectants, the parental cells, and neomycin vector-transfected control cells at 37 degrees C. Following a temperature shift to 32 degrees C, the **p53** transfectants rapidly lost viability, and 95-100% of the cells were dead by 3 days, whereas the control cells remained unaffected. Examination of DNA isolated from **p53**-transfected cells grown at 32 degrees C revealed nucleosomal fragmentation, indicating cell death by apoptosis. It is suggested that apoptosis is triggered by contradictory signaling. Constitutively expressed v-myc can stimulate cell proliferation, whereas expression of wild-type **p53** in cells that have lost endogenous **p53** expression in the course of their neoplastic development may suppress growth.

L5 ANSWER 3 OF 5 MEDLINE
ACCESSION NUMBER: 93275643 MEDLINE
DOCUMENT NUMBER: 93275643 PubMed ID: 8502475
TITLE: Wild-type p53 induces apoptosis in a Burkitt lymphoma (BL) line that carries mutant p53.
AUTHOR: Ramqvist T; Magnusson K P; Wang Y; Szekely L; Klein G; Wiman K G
CORPORATE SOURCE: Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.
CONTRACT NUMBER: 5R01 CA14054 (NCI)
SOURCE: ONCOGENE, (1993 Jun) 8 (6) 1495-500.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930716
Last Updated on STN: 19980206
Entered Medline: 19930629

AB All Burkitt lymphoma (BL) biopsies and cell lines carry a c-myc/Ig translocation. The resulting constitutive activation of c-myc is regarded as an essential factor for the progressive growth of the tumor cells. At least 60% of BL cell lines carry a mutated **p53** gene as well. It has been shown that the growth of mutant **p53** carrying tumor cells could be inhibited by the introduction of wild-type **p53**. In order to examine whether this also applies to the presumably 'myc-driven' BL cell, we have transfected the Epstein-Barr virus (EBV) negative BL41 cell line with a temperature sensitive **p53** mutant (**p53-Val135**) that expresses **p53** with a largely mutant conformation at 37.5 degrees C and mostly wild-type conformation at 32 degrees C. At 37.5 degrees C, the **p53-Val135** transfected cells behaved like the parental or neo transfected control cells. However, expression of exogenous wild-type **p53** at 32 degrees C resulted in a rapid reduction of the number of viable cells while the parental and neo control cells remained unaffected. Cell death was due to apoptosis as shown by chromatin and nuclear condensation and specific DNA fragmentation. The first signs of apoptosis were evident after 10 h at 32 degrees C and after 3 days 90-100% of the cells had undergone apoptosis. These findings indicate an incompatibility between expression of wild-type **p53** and progressive growth of BL cells if their neoplastic development has included a **p53** mutation. The question whether apoptosis was induced in by the wild-type protein per se or by the contradictory signals of a constitutively activated c-myc and wild-type **p53** needs further investigation.

L5 ANSWER 1 OF 5 MEDLINE
ACCESSION NUMBER: 94067793 MEDLINE
DOCUMENT NUMBER: 94067793 PubMed ID: 8247545
TITLE: Cell-type- and promoter-dependent ts phenotype of **p53 Val135**.
AUTHOR: Sehgal P B; Margulies L
CORPORATE SOURCE: Department of Microbiology and Immunology, New York Medical College, Valhalla 10595.
SOURCE: ONCOGENE, (1993 Dec) 8 (12) 3417-9.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940201
Last Updated on STN: 19980206
Entered Medline: 19931229

AB The **p53** mutant **Val135** is widely considered to have a wild-type (wt) phenotype at 32.5 degrees C, but not at 37 degrees C. The ability of wt murine **p53** and its **Val135** mutant to modulate transcription from the muscle-specific creatine kinase promoter (-3.3 kb pMCK), from a reporter construct containing two copies of the **p53**-binding DNA element from within MCK (p50-2), and from the interleukin-6 (IL-6) promoter (pIC225) was evaluated in transient transfection experiments in CV1 and HeLa cells. In CV1 cells, wt **p53** was confirmed to activate the pMCK and p50-2 reporters, but to repress the IL-6 promoter. However, although in these cells **p53 Val135** had the expected wt-like phenotype with respect to activation of the p50-2 reporter at 32.5 degrees C (32.5 degrees C > 37 degrees C), this mutant had little effect on expression from pMCK at either temperature, and activated rather than repressed the IL-6 promoter at 32.5 degrees C. In HeLa cells, although wt **p53** activated p50-2 but repressed the MCK and IL-6 promoters, **p53 Val135** activated all three reporters. Unexpectedly, in these cells the upregulation of p50-2 and pIC225 was basically temperature-independent, and that of pMCK was inversely ts (37 degrees C > 32.5 degrees C). The novel ts properties of **p53 Val135** show that this mutant is not always wt-like at 32.5 degrees C but exhibits strong cell-type and promoter-dependent differences in its ts phenotype for transcriptional modulation.

L5 ANSWER 2 OF 5 MEDLINE
ACCESSION NUMBER: 93385051 MEDLINE
DOCUMENT NUMBER: 93385051 PubMed ID: 8373731
TITLE: Reconstitution of wild-type p53 expression triggers apoptosis in a p53-negative v-myc retrovirus-induced T-cell lymphoma line.
AUTHOR: Wang Y; Ramqvist T; Szekely L; Axelson H; Klein G; Wiman K G
CORPORATE SOURCE: Department of Tumor Biology, Karolinska Institute, Stockholm, Sweden.
CONTRACT NUMBER: CA14054 (NCI)
SOURCE: CELL GROWTH AND DIFFERENTIATION, (1993 Jun) 4 (6) 467-73.
Journal code: AYH; 9100024. ISSN: 1044-9523.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931105
Last Updated on STN: 19970203
Entered Medline: 19931021

AB Inactivation or mutation of the **p53** tumor suppressor gene has been observed in a wide variety of human and murine tumors. We have found

L5 ANSWER 4 OF 5 MEDLINE
ACCESSION NUMBER: 91354778 MEDLINE
DOCUMENT NUMBER: 91354778 PubMed ID: 1953903
TITLE: The role of p53 in the normal control of cell proliferation.
COMMENT: Erratum in: Curr Opin Cell Biol 1991 Jun;3(3):following 574
AUTHOR: Milner J
CORPORATE SOURCE: Department of Pathology, University of Cambridge, UK.
SOURCE: CURRENT OPINION IN CELL BIOLOGY, (1991 Apr) 3 (2) 282-6.
Ref: 20
Journal code: AOE; 8913428. ISSN: 0955-0674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911027
Last Updated on STN: 19911027
Entered Medline: 19911004

AB The regulation of cell proliferation involves **p53**. A mutant allele of **p53, p53-Val135,** has been found to be temperature-sensitive for function with separable suppressor and promoter effects on cell proliferation. These opposing suppressor and promoter functions of **p53** correlate with two alternative, temperature-sensitive conformations of the **p53-Val135** polypeptide.

L5 ANSWER 5 OF 5 MEDLINE
ACCESSION NUMBER: 91080136 MEDLINE
DOCUMENT NUMBER: 91080136 PubMed ID: 2258922
TITLE: Temperature-dependent switching between "wild-type" and "mutant" forms of **p53-Val135**.
AUTHOR: Milner J; Medcalf E A
CORPORATE SOURCE: Department of Pathology, University of Cambridge, U.K.
SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (1990 Dec 5) 216 (3) 481-4.
Journal code: J6V; 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910322
Last Updated on STN: 19910322
Entered Medline: 19910131

AB The **p53** gene is a suppressor of abnormal cell growth but is also subject to oncogenic activation by mutation. The mutant allele **p53-Val135,** has recently been discovered to be temperature-sensitive and functions as an oncogene at 37 degrees C and as a tumor suppressor at 32.5 degrees C. In order to investigate the molecular mechanism underlying the temperature sensitivity of **p53-Val135** rabbit reticulocyte lysate was used to translate the **p53** mRNAs in vitro at 37 degrees C and at 30 degrees C. The immunoreactivity and T antigen binding of wild-type protein **p53** -Ala135 were unaffected by temperature and were similar to wild-type **p53** expressed in vivo. In contrast, the mutant **p53-Val135** protein was markedly affected by temperature. At 37 degrees C **p53-Val135** showed reduced T antigen binding and did not react with monoclonal antibodies PAb246 and PAb1620. At 30 degrees C, **p53-Val135** behaved as the wild-type **p53**. Temperature also exerted a post-translational effect on **p53-Val135** with complete conversion from wild-type to mutant phenotype within two minutes of temperature shift from 30 degrees C to 37 degrees C. There was incomplete conversion from mutant to wild-type phenotype when

the temperature was shifted down from 37 degrees C to 30 degrees C. We propose that the temperature dependent forms of **p53-Val135** represent conformational variants of the **p53** protein with opposing functions in cell growth control.

L3 ANSWER 3 OF 3 MEDLINE
ACCESSION NUMBER: 93016320 MEDLINE
DOCUMENT NUMBER: 93016320 PubMed ID: 1400626
TITLE: Wild-type murine p53 represses transcription from the murine c-myc promoter in a human glial cell line.
AUTHOR: Moberg K H; Tyndall W A; Hall D J
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Thomas Jefferson University, Philadelphia, Pennsylvania 19107.
CONTRACT NUMBER: CA51170 (NCI)
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (1992 Jun) 49 (2) 208-15.
Journal code: HNF; 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19980206
Entered Medline: 19921123

AB Here we analyzed the effect of the suppressor proto-oncogene p53 on transcription from the P2 promoter of the murine c-myc gene. c-myc promoter constructs were coupled to the chloramphenicol acetyl-transferase (CAT) gene and were transiently transfected into a human **glial cell** along with plasmids overexpressing wild-type or **mutant p53**. It was found that significant repression of c-myc transcription took place following cotransfection with wild-type but not **mutant p53**. However wild-type p53 did not suppress transcription from the SV40 early promoter or from the MHC promoter. Promoter-CAT constructs containing only the ME1a2 or E2F elements, from the P2 promoter, were repressed by p53, indicating that p53 may exert its effect at these two sites within the P2 promoter. Finally, when the SV40 T antigen and wild-type p53 were expressed together in **glial cells** the repressive effect of p53 was abolished.

L10 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:70745 CAPLUS
DOCUMENT NUMBER: 120:70745
TITLE: Cell-type- and promoter-dependent ts phenotype of **p53 Val135**
AUTHOR(S): Sehgal, Pravin B.; Margulies, Lola
CORPORATE SOURCE: Dep. Microbiol. Immunol., New York Med. Coll., Valhalla, NY, 10595, USA
SOURCE: Oncogene (1993), 8(12), 3417-19
CODEN: ONCNES; ISSN: 0950-9232
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **p53** mutant **Val135** is widely considered to have a wild-type (wt) phenotype at 32.5.degree., but not at 37.degree.. The ability of wt murine **p53** and its **Val135** mutant to modulate transcription from the muscle-specific creatine kinase promoter (-3.3 kb pMCK), from a reporter construct contg. two copies of the **p53**-binding DNA element from within MCK (p50-2), and from the interleukin-6 (IL-6) promoter (pIC225) was evaluated in transient transfection expts. in CV1 and HeLa cells. In CV1 cells, wt **p53** was confirmed to activate the pMCK and p50-2 reporters, but to repress the IL-6 promoter. However, although in these cells **p53** **Val135** had the expected wt-like phenotype with respect to activation of the p50-2 reporter at 32.5.degree. (32.5.degree. > 37.degree.), this mutant had little effect on expression from pMCK at either temp., and activated rather than repressed the IL-6 promoter at 32.5.degree.. In HeLa cells, although wt **p53** activated p50-2 but repressed the MCK and IL-6 promoters, **p53 Val135** activated all 3 reporters. Unexpectedly, in these cells the up-regulation of p50-2 and pIC225 was basically temp.-independent, and that of pMCK was inversely ts (37.degree. < 32.5.degree.). The novel ts properties of **p53 Val135** show that this mutant is not always wt-like at 32.5.degree. but exhibits strong cell-type and promoter-dependent differences in its ts phenotype for transcriptional modulation.

L10 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:622963 CAPLUS
DOCUMENT NUMBER: 119:222963
TITLE: Wild-type p53 induces apoptosis in a Burkitt lymphoma (BL) line that carries mutant p53
AUTHOR(S): Ramqvist, Torbjoern; Magnusson, Kristinn P.; Wang, Yisong; Szekely, Laszlo; Klein, George; Wiman, Klas G.
CORPORATE SOURCE: Dep. Tumor Biol., Karolinska Inst., Stockholm, S-104 01, Swed.
SOURCE: Oncogene (1993), 8(6), 1495-500
CODEN: ONCNES; ISSN: 0950-9232
DOCUMENT TYPE: Journal
LANGUAGE: English
AB All Burkitt lymphoma (BL) biopsies and cell lines carry a c-myc/Ig translocation. The resulting constitutive activation of c-myc is regarded as an essential factor for the progressive growth of the tumor cells. At least 60% of BL cell lines carry a mutated **p53** gene as well. It has been shown that the growth of mutant **p53** carrying tumor cells could be inhibited by the introduction of wild-type **p53**. To examine whether this also applies to the presumably 'myc-driven' BL cell, the authors have transfected the Epstein-Barr virus (EBV) neg. BL41 cell line with a temp. sensitive **p53** mutant (**p53-Val135**) that expresses **p53** with a largely mutant conformation at 37.5.degree. and mostly wild-type conformation at 32.degree.. At 37.5.degree., the **p53-Val135** transfected cells behaved like the parental or neo transfected control cells. However, expression of exogenous wild-type **p53** at 32.degree. resulted in a rapid redn. of the no. of viable cells, whereas the parental and neo control cells remains unaffected. Cell death was due to apoptosis as shown by chromatin and nuclear condensation and specific

DNA fragmentation. The first signs of apoptosis were evident after 10 h at 32.degree. and after 3 days 90-100% of the cells had undergone apoptosis. These findings indicate an incompatibility between expression of wild-type **p53** and progressive growth of BL cells if their neoplastic development has included a **p53** mutation. The question whether apoptosis was induced in by the wild-type protein per se or by the contradictory signals of a constitutively activated c-myc and wild-type **p53** needs further investigation.

L10 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:646625 CAPLUS
DOCUMENT NUMBER: 119:246625
TITLE: Reconstitution of wild-type p53 expression triggers apoptosis in a p53-negative v-myc retrovirus-induced T-cell lymphoma line
AUTHOR(S): Wang, Yisong; Ramqvist, Torbjorn; Szekely, Laszlo; Axelson, Haakan; Klein, George; Wiman, Klas G.
CORPORATE SOURCE: Dep. Tumor Biol., Karolinska Inst., Stockholm, S-104 01, Swed.
SOURCE: Cell Growth Differ. (1993), 4(6), 467-73
CODEN: CGDIE7; ISSN: 1044-9523
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Inactivation or mutation of the **p53** tumor suppressor gene has been obsd. in a wide variety of human and murine tumors. The authors have found that a v-myc retrovirus (J3)-induced T-cell lymphoma line (J3D) has lost one of its **p53** alleles, whereas the other has become inactivated due to the insertion of a Moloney murine leukemia provirus in intron 4 with an opposite transcriptional orientation. No **p53** protein could be detected by immunopptn. with monoclonal anti-**p53** antibodies. The authors have transfected this line with the temp.-sensitive murine **Val135** construct that is expressed as mutant **p53** at 37.degree. and largely wild-type **p53** at 32.degree.. There was no difference in the no. of viable cells among the **p53** transfectants, the parental cells, and neomycin vector-transfected control cells at 37.degree.. Following a temp. shift to 32.degree., the **p53** transfectants rapidly lost viability, and 95-100% of the cells were dead by 3 days, whereas the control cells remained unaffected. Examn. of DNA isolated from **p53** -transfected cells growth at 32.degree. revealed nucleosomal fragmentation, indicating cell death by apoptosis. It is suggested that apoptosis is triggered by contradictory signaling. Constitutively expressed v-myc can stimulate cell proliferation, whereas expression of wild-type **p53** in cells that have lost endogenous **p53** expression in the course of their neoplastic development may suppress growth.

L10 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:551979 CAPLUS
DOCUMENT NUMBER: 115:151979
TITLE: The role of p53 in the normal control of cell proliferation
AUTHOR(S): Milner, Jo
CORPORATE SOURCE: Univ. Cambridge, Cambridge, CB2 1QP, UK
SOURCE: Curr. Opin. Cell Biol. (1991), 3(2), 282-6
CODEN: COCBE3; ISSN: 0955-0674
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 20 refs. The regulation of cell proliferation involves **p53**. A mutant allele of **p53**, **p53-Val135**, has been found to be temp.-sensitive for function with separable suppressor and promoter effects on cell proliferation. These opposing suppressor and promoter functions of **p53** correlate with two alternative, temp.-sensitive conformations of the **p53-Val135** polypeptide.

L10 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:96973 CAPLUS
DOCUMENT NUMBER: 114:96973
TITLE: Temperature-dependent switching between "wild-type" and "mutant" forms of **p53-Val135**
AUTHOR(S): Milner, J.; Medcalf, E. A.
CORPORATE SOURCE: Dep. Pathol., Univ. Cambridge, Cambridge, CB2 1QP, UK
SOURCE: J. Mol. Biol. (1990), 216(3), 481-4
CODEN: JMOBAK; ISSN: 0022-2836
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **p53** gene is a suppressor of abnormal cell growth but is also subject to oncogenic activation by mutation. The mutant allele **p53-Val135,** has recently been discovered to be temp.-sensitive and functions as an oncogene at 37.degree. and as a tumor suppressor at 32.5.degree.. In order to investigate the mol. mechanism underlying the temp. sensitivity of **p53-Val135,** rabbit reticulocyte lysate was used to translate the **p53** mRNAs in vitro at 37.degree. and at 30.degree.. The immunoreactivity and T antigen binding of wild-type protein **p53**-Ala135 were unaffected by temp. and were similar to wild-type **p53** expressed in vivo. In contrast, the mutant **p53-Val135** protein was markedly affected by temp. At 37.degree. **p53-Val135** showed reduced T antigen binding and did not react with monoclonal antibodies PAb246 and PAb1620. At 30.degree., **p53-Val135** behaved as the wild-type **p53**. Temp. also exerted a post-translational effect on **p53-Val135** with complete conversion from wild-type to mutant phenotype within two minutes of temp. shift from 30.degree. to 37.degree.. There was incomplete conversion from mutant to wild-type phenotype when the temp. was shifted down from 37.degree. to 30.degree.. It is proposed that the temp. dependent forms of **p53 -Val135** represent conformational variants of the **p53** protein with opposing functions in cell growth control.

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PROCESSING COMPLETED FOR L7
L8           15 DUP REM L7 (14 DUPLICATES REMOVED)

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L9            4 L8 NOT PY>1994

=> d 1-4 ibib abs

L9   ANSWER 1 OF 4     MEDLINE
ACCESSION NUMBER:    94267889     MEDLINE
DOCUMENT NUMBER:     94267889   PubMed ID: 8207805
TITLE:               The tumor suppressor protein p53 strongly alters human
                     immunodeficiency virus type 1 replication.
AUTHOR:              Duan L; Ozaki I; Oakes J W; Taylor J P; Khalili K;
                     Pomerantz R J
CORPORATE SOURCE:    Dorrance H. Hamilton Laboratories, Department of Medicine,
                     Jefferson Medical College, Thomas Jefferson University,
                     Philadelphia, Pennsylvania 19107.
CONTRACT NUMBER:     AI31836 (NIAID)
                     NS30916 (NINDS)
SOURCE:              JOURNAL OF VIROLOGY, (1994 Jul) 68 (7) 4302-13.
                     Journal code: KCV; 0113724. ISSN: 0022-538X.
PUB. COUNTRY:        United States
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         199407
ENTRY DATE:          Entered STN: 19940721
                     Last Updated on STN: 19970203
                     Entered Medline: 19940713
AB   The p53 tumor suppressor gene product, a sequence-specific DNA-
     binding protein, has been shown to act as a transcriptional
     activator and repressor both in vitro and in vivo. Consistent with its
     role in regulating transcription are recent observations that the
     N-terminal acidic domain of p53 binds directly to the TATA box-binding
     protein subunit of the general transcription factor, TF IID. It is now
     demonstrated that wild-type p53 (wt-p53) inhibits human immunodeficiency
     virus type 1 (HIV-1) long terminal repeat (LTR)-directed
     chloramphenicol acetyltransferase activity in a cotransfection assay
     system. Importantly, this effect of wt-p53 on the HIV-1 LTR was also
     demonstrated by in vitro transcription assays. In addition, the Sp1 sites
     and the TATA box of the HIV-1 LTR are demonstrated to be the primary sites
     involved with p53-induced effects on this viral promoter. The upstream
     elements of the HIV-1 LTR, including the nuclear factor kappa B (NF-kappa
     B) binding sites, decrease the p53-induced inhibitory effects on viral
     transcription. In the presence of the HIV-1 TAR sequence and Tat protein,
     the HIV-1 LTR also becomes less sensitive to wt-p53-induced inhibition. By
     using a retroviral vector delivery system, mutant forms of p53 genes were
     expressed in two HIV-1 latently infected cell lines, ACH-2 and U1. In the
     ACH-2 cell line, which is now demonstrated to contain an endogenous mutant
     form of p53 (amino acid 248, Arg to Gln), additional mutant
     p53 proteins did not alter HIV-1 replication. In U1 cells, which
     completely lack endogenous p53, overexpression of mutant
     p53 led to an increase in HIV-1 replication. Thus, these data
     indicate a possible functional role for wt-p53 and mutant
     p53 proteins in the control of HIV-1 replication patterns and
     proviral latency.

L9   ANSWER 2 OF 4     MEDLINE
ACCESSION NUMBER:    94020823     MEDLINE
DOCUMENT NUMBER:     94020823   PubMed ID: 8414502
TITLE:               Analysis of p53 transactivation through high-affinity
                     binding sites.
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AUTHOR: Chumakov A M; Miller C W; Chen D L; Koeffler H P
CORPORATE SOURCE: Cedars-Sinai Medical Center, UCLA School of Medicine 90048.
SOURCE: ONCOGENE, (1993 Nov) 8 (11) 3005-11.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19980206
Entered Medline: 19931124

AB Alterations or elimination of the p53 protein is frequently occurring during human carcinogenesis. Overexpression of wild-type p53 has a profound growth-inhibitory effect on many cell lines, including strong and apparently non-sequence specific repression of a number of promoters. Consistent with the hypothesis that it acts as transcriptional regulator, wild-type p53 protein binds DNA and activates transcription of several promoters. We have studied **DNA binding** and transactivation (TA) properties of human wild-type and **mutant p53** proteins representing four major mutational hotspots. DNA-gel retardation was used to detect specific p53-DNA complexes in nuclear extracts, with radiolabelled oligonucleotides representing high affinity p53-binding sites (HBS) as a probe. p53-specific complexes were identified by competition with unlabelled 'self' oligos and by double band-shifts in the presence of anti-p53 antibodies. To show transactivation by p53, TK promoter-driven CAT reporter gene was placed 3' of the p53-binding site. CAT activity was assayed after co-transfection of reporters with either wild-type (WT) or **mutant p53** expression constructs into human cells that do not express p53 (SKOV3). We found that wild-type p53 has strong transactivating effect on the reporter. All mutants, with the exception of His273, were inactive in TA-assay. p53 is a target of several oncogenes found in DNA tumor **viruses**. We examined the effect of either SV40 T-ag or 55 kDa E1B protein of Ad5 on **DNA binding** and transactivation by p53 in transformed COS-1 and 293 cell lines, respectively. COS-1 extracts produced strong p53-dependent band-shift of the HBS oligos, that was doubleshifted by anti-p53 but not anti-T-ag antibodies, indicating that T-ag is not part of the complex. COS-1 cells had a high level of WT p53-dependent expression of transfected CAT reporter, indicating the presence of transactivation-competent p53, acting through the HBS element. In human Ad-transformed 293 cells, endogenous p53 was also transactivation competent and capable of **DNA binding**. In summary, we found efficient transactivation of HBS motif by WT and His273-p53. Studies of COS-1 and 293 cells suggest that a proportion of p53 in transformed cells display wild-type **DNA binding** and TA properties and that expression of transcriptionally inactive **mutant p53** proteins in these cells does not interfere with WT-dependent transactivation.

L9 ANSWER 3 OF 4 MEDLINE
ACCESSION NUMBER: 93360955 MEDLINE
DOCUMENT NUMBER: 93360955 PubMed ID: 8355677
TITLE: Functional domains of wild-type and mutant p53 proteins involved in transcriptional regulation, transdominant inhibition, and transformation suppression.
AUTHOR: Unger T; Mietz J A; Scheffner M; Yee C L; Howley P M
CORPORATE SOURCE: Laboratory of Tumor Virus Biology, National Cancer Institute, Bethesda, Maryland 20892.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1993 Sep) 13 (9) 5186-94.
Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309